DOCKET NO. 7732-022-27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF: Beth P. GOLDSTEIN, et al. ART UNIT: 1631
SERIAL NO.: 09/120,030 EXAMINER: Michael L. Borin
FILING DATE: July 21, 1998
FOR: METHOD FOR THE TREATMENT OF STAPHYLOCOCCAL DISEASE

APPEAL BRIEF

ASSISTANT COMMISSIONER FOR PATENTS
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SIR:

This is an Appeal under 37 C.F.R. §1.192 from the Final Rejection dated September 17, 2004. Each of the topics required under Rule 192 is presented herewith and is labeled appropriately.

I. REAL PARTY IN INTEREST

The real party in interest in this patent application is Nutrition 21, Inc.

II. RELATED APPEALS AND INTERFERENCES

The Applicants know of no related appeals or interferences that will directly affect, will be directly affected, or have any bearing on the Board's decision in this Appeal.

III. STATUS OF CLAIMS

Claims 4, 5, 28, 32, 35, 44-51, 56-59 and 61-66 are currently pending. Claims 28 and 35 have been withdrawn. The rejection of Claims 4, 5, 32, 44-51, 56-59 and 61-66 is being appealed. In the Office Action Summary mailed on September 17, 2004, Claims 4, 5, 28, 32, 35, 41-51, 56-59 and 61-66 are listed as pending. However, an Amendment After Final was filed on October 20, 2003 canceling Claims 36-43. This amendment was entered upon the filing of a Request for Continued Examination on November 26, 2003 (See page 2 of the Official Action mailed on February 20, 2004). Therefore, Claims 41-43 have been canceled and Claims 4, 5, 28, 32, 35, 44-51, 56-59 and 61-66 are currently pending.

IV. STATUS OF AMENDMENTS

No amendments have been made subsequent to the mailing of date of the Final Office Action currently being appealed (*i.e.*, September 17, 2004).

V. SUMMARY OF THE INVENTION

According to one embodiment, the present invention is directed to a method of treating an established staphylococcal infection of at least one organ or tissue selected from the group consisting of heart valve, blood, kidney, lung, bone and meninges, comprising systemically administering to a human suffering from at least one of said infections an effective amount of at least one recombinantly produced lysostaphin analogue, wherein multiple doses of the lysostaphin analogue are administered and wherein the amount of lysostaphin analogue(s) administered is from 0.5 to 30 mg/kg/day.

According to a further embodiment, the present invention is directed to a method of treating an established infection associated with a catheter or a prosthetic device, comprising

systemically administering to a human suffering from such an infection an effective amount of at least one recombinantly produced lysostaphin analogue wherein multiple doses of the lysostaphin analogue are administered and wherein the amount of lysostaphin analogue(s) administered is from 0.5 to 30 mg/kg/day.

VI. ISSUES

The issues presented for review are as follows:

(1) whether Claims 4, 5, 32, 41-51, 56-59 and 61-66 are patentable under 35 U.S.C. §103(a) over Zygmunt and Goldberg and Stark, and further in view of Oldham; and

(2) whether Claims 32, 42, 43, 46, 47, 50, 51, 54 and 55 are patentable under 35 U.S.C. §103(a) over Zygmunt and Goldberg and Stark, and Oldham and further in view of Dixon.

VII. GROUPING OF CLAIMS

For purposes of this appeal only, Claims 4, 5, 32, 56-59, 65 and 66 stand or fall together. Claims 44-51 are separately patentable from Claims 4, 5, 32, 56-59, 65 and 66 and therefore do not stand or fall together with Claims 4, 5, 32, 56-59, 65 and 66. In particular, Claims 4, 5, 32, 56-59, 65 and 66 recite that the amount of lysostaphin analogue(s) administered is from 0.5 to 30 mg/kg/day. In contrast, Claims 44-51 recite that the amount of lysostaphin analogue(s) administered is from 0.5 to *25* mg/kg/day. According to the Official Action, the rejection of each of these claims relies on the degree of difference in the dosages described as effective in dogs as set forth in the Goldberg reference compared to the dosage ranges set forth in these claims. All of the dosages disclosed in the Goldberg reference and described as being effective in dogs exceeded 30 mg/kg/day. However, since the upper limits on the dosage ranges recited in each of the aforementioned groupings of claims are different, the extent of this difference necessarily

varies for each of these claim groupings. Since an obviousness determination may depend on the differences between the claimed dosage range and the dosages disclosed in the Goldberg reference and since the degree of difference varies for each claim grouping, it is respectfully submitted these claims do not stand or fall together.

Claims 61-64 also do not stand or fall together with the remaining claims. These claims recite either that the infection is cleared or that the treatment results in complete sterilization of the infection. As set forth below, one of ordinary skill in the art as of the effective filing date of the application would not have expected complete sterilization of an infection to result from administration of lysostaphin analogue(s) in an amount of 0.5 to 30 mg/kg/day or 0.5 to 25 mg/kg/day. Moreover, the Goldberg reference discloses that treatments of dogs with dosages in the claimed range resulted in the development of resistant strains and eventual relapse. Accordingly, Claims 61-64 also do not stand or fall together with the remaining claims.

VIII. ARGUMENT

Claims 4, 5, 32, 41-51, 56-59 and 61-66 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Zygmunt and Goldberg and Stark, and further in view of Oldham. This rejection, which appears on pages 2-3, numbered paragraph 3 of the Official Action, is respectfully traversed.

The Examiner has acknowledged that the dosage ranges recited in Claims 4 and 5 do not embrace any of the dosages administered to dogs listed as "well" or "improved" in Goldberg. Moreover, the Official Action mailed September 17, 2004 states that "there is only a marginal difference between dosages described as effective on dogs in Goldberg and dosage range as instantly claimed" (page 2 of the Official Action mailed September 17, 2004). The Official Action is apparently referring to the dosages administered to dogs 4 and 5 of 31.6 and 35.4

mg/kg/day in Goldberg compared to the upper limit of 30 mg/kg/day set forth in Claims 4 and 5 (sentence bridging pages 3-4 of the Official Action mailed February 20, 2004). The Official Action then asserts that "[a]bsent some teaching to the contrary (which is still not offered by applicant) determination of particular ranges employed is within the skill of the ordinary worker as a part of the process of normal optimization" (sentence bridging pages 2-3 of the Official Action mailed September 17, 2004). The Examiner has therefore acknowledged that the dosage ranges recited in Claims 4 and 5 do not embrace any of the dosages administered to dogs listed as "well" or "improved" in Goldberg. Instead, the Official Action is relying on the alleged closeness of the dosage range recited in the claims compared to the actual dosages administered to dogs 4 and 5 which were included in the group of "well dogs" in Goldberg.

A *prima facie* case of obviousness can be established where a claimed range and a prior art range do not overlap but *are close enough that one skilled in the art would have expected them to have the same properties* {See MPEP §2144.05(I)}. Goldberg, however, clearly teaches that dosages in the claimed range do not achieve the same result as the higher dosages but, rather, result in an unacceptable increase in resistant strains and eventual relapse of the dogs being treated. In particular, Goldberg observed the development of lysostaphin resistant bacterial strains in the dogs being studied. According to Goldberg, "[t]he largest proportions of isolates found to be resistant were in three dogs receiving small repeated doses" of lysostaphin (page 52 of Goldberg). Referring back to Table 4 of Goldberg, which summarizes the lysostaphin resistance data, it can be clearly seen that the dogs being referred to in this excerpt from Goldberg include dogs 7 and 10 which had 83 and 66 % lysostaphin resistant strains, respectively, after treatment (page 50 of Goldberg)[1]. It should be noted that dogs 7 and 10 were administered

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[1] The fact that Goldberg is referring to dogs 7 and 10 can be clearly seen from page 51 of that reference which recites as follows:

dosages within the range recited in Claims 4 and 5. Further, Goldberg postulates that "[t]he emergence of resistant isolates in these dogs may have resulted from repeated exposure to small amounts of enzyme" and that "[t]hese three dogs relapsed, perhaps as a result of the large proportion of resistant staphylococci, or perhaps because the small doses of enzyme were insufficient to control the infection" (page 52 of Goldberg). As a result, one skilled in the art would not have expected dosages in the claimed range to have the same properties as the higher dosages administered to dogs in the "well" and "improved" groups in Goldberg.

It is also respectfully submitted that Goldberg teaches away from the invention as set forth in Claims 4 and 5. In particular, the disclosure in Goldberg that the administration of dosages of lysostaphin within the claimed range *to dogs* resulted in the development of resistant strains and to eventual relapse whereas higher dosages outside the claimed range resulted in recovery teaches away from the administration of dosages as set forth in Claims 4 and 5 to humans. According to the MPEP, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. In re Geisler, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). MPEP §2144.05(III). Moreover, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (See MPEP §2141.02). It is respectfully submitted that these clear teachings in Goldberg would lead one of skill in the art away from the methods of treatment defined by Claims 4 and 5 of the instant application. In view of the above, reconsideration and withdrawal of the rejections of Claims 4 and 5 is therefore respectfully

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"[t]he highest proportions of resistant isolates after treatment were found in four of five relapsed dogs. Three of these dogs had received the smallest repeated doses of enzyme."

requested.

The Official Action mailed September 17, 2004 asserts that " . . . *it would be obvious* that determination of particular ranges of recombinant lysostaphin for use in humans would be within the skill of the ordinary worker as part of the process of normal optimization" (emphasis added, page 3 of the Official Action mailed September 17, 2004). The Official Action has applied the wrong legal standard. As set forth in 35 U.S.C. §103(a), obviousness is determined *at the time the invention was made.* Accordingly, "it is . . . necessary that the decision maker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made . . ." See MPEP §2141.01(III). Accordingly, what is allegedly obvious now is not relevant to the obviousness inquiry. The Official Action also states that "[the] instant specification itself supports the obviousness to determine a particular dosage range . . ." It is well established, however, that the teaching or suggestion to make the claimed combination must be found in the prior art and not be based on applicant's disclosure. See MPEP §2142. Thus, it is improper for the Official Action to rely upon the applicant's disclosure to establish or "support" a *prima facie* case of obviousness. Moreover, as set forth above, various teachings in Goldberg would lead one of skill in the art away from the methods of treatment defined by Claims 4 and 5 of the instant application. As set forth in the MPEP, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See MPEP §2144.05(III).

Claims 4 and 5 also recite the administration to humans of *recombinantly* produced lysostaphin. Neither Zygmunt, Stark and Goldberg disclose systemic treatment of humans using *recombinant* lysostaphin. Indeed, Zygmunt and Goldberg relate to treating staphylococcal infections in animals such as dogs and mice using lysostaphin. While Stark discloses treatment in a human, the study involved a single human and is more speculative of treatment in humans

than conclusive, as indicated by the article's title (*i.e.*, "Systemic Lysostaphin in Man - Apparent Antimicrobial Activity in a Neutropenic Patient"). Moreover, the patient in Stark died three days after administration of the lysostaphin, making long-term study impossible. In addition, the Examiner has previously acknowledged that Zygmunt, Stark and Goldberg do not teach *recombinant* lysostaphin or the use thereof (See the Office Action mailed September 20, 2002, page 6). The Examiner instead relies on Oldham to remedy this acknowledged deficiency of Zygmunt, Stark and Goldberg. Moreover, the Official Action relies upon Oldham to "demonstrate that lysostaphin can be produced recombinantly and that the product produced thereby has high antimicrobial activity similar to that of the natural product" (See the Office Action mailed September 20, 2002, page 6).

It is respectfully submitted, however, that Oldham does not remedy the acknowledged deficiencies of Zygmunt, Stark and Goldberg. First, Oldham is limited to the treatment of a specific staphylococcal infection not found in humans, namely bovine mastitis. As discussed by Michael Climo, M.D. in a Declaration under 37 C.F.R. § 1.132 dated September 27, 2001, the treatment of bovine mastitis is not predictive of treatment of staphylococcal infections in humans (See Climo Declaration, page 3, ¶ 11). A copy of the Climo Declaration, which was filed on October 4, 2001, is submitted herewith. Second, Oldham discloses that recombinant lysostaphin is highly immunogenic in systemic administration (See pages 4181-4182 of Oldham). This disclosure alone is sufficient to teach away from the instant invention (See Climo Declaration, page 4, ¶ 13). In fact, the very method identified by Oldham as posing problems with immunogenicity (*i.e.*, parenteral administration) is precisely the method taught by the primary references cited in the Official Action (See, for example, Zygmunt, page 237). Whatever the primary references may or may not teach about naturally-occurring lysostaphin, it is clear from the teachings of the cited references that recombinant lysostaphin is immunogenic when

administered systemically. Third, the data suggests that even if recombinant lysostaphin is administered locally, curing of the staphylococcal infection does not ensue in a high percentage of the cases (See, for example, Oldham, page 4180, Table 3). For at least the aforementioned reasons, it is respectfully submitted that one of ordinary skill in the art would not have been motivated, based on the teachings of Oldham, to modify the Zygmunt, Stark and Goldberg references to arrive at the claimed invention.

Claims 32, 41-51 and 56-59 and 61-66 depend either directly or indirectly from Claims 4 or 5 and are therefore also patentable for at least the reasons set forth above with respect to Claims 4 and 5. Accordingly, it is respectfully requested that the rejection of Claims 32, 41-51 and 56-59 and 61-66 be reconsidered and withdrawn.

In addition, Claims 44-51 can be further distinguished from the references of record. These claims recite dosages of *up to 25 mg/kg/day*. These dosages are substantially lower than any dosage administered to a "well" or "improved" dog in Goldberg. In particular, the lowest dosage administered to a "well" or "improved" dog in Goldberg (*i.e.*, 31.6 mg/kg/day) is 26.4 percent greater than the upper limit of the recited dosage range. It is respectfully submitted that, in view of the above, the subject matter of these claims can be further distinguished from the cited references.

Claims 61-64 can also be further distinguished from the references of record. These claims recite either that the infection is cleared or that the treatment results in complete sterilization of the infection. As set forth below, one of ordinary skill in the art as of the effective filing date of the application would not have expected complete sterilization of an infection to result from administration of lysostaphin analogue(s) in an amount of 0.5 to 30 mg/kg/day or 0.5 to 25 mg/kg/day. Moreover, the Goldberg reference discloses that treatments of dogs with dosages in the claimed range resulted in the development of resistant strains and eventual relapse.

It is respectfully submitted that, in view of the above, the subject matter of these claims can be further distinguished from the cited references.

Claims 32, 42, 43, 46, 47, 50, 51, 54 and 55 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Zygmunt and Goldberg and Stark, and Oldham and further in view of Dixon. This rejection, which appears on page 5, numbered paragraph 5 of the Official Action, is respectfully traversed.

As set forth above, Zygmunt and Goldberg and Stark, and Oldham fail to teach or reasonably suggest the method as set forth in Claims 4 or 5. Claims 32 and 58 depend from Claims 4 and 5, respectively, and further recite administering a second antimicrobial agent selected from the group consisting of rifamycin, a glycopeptide, and combinations thereof. Dixon, however, is merely being relied upon for teaching the use of lysostaphin in combination with other anti-microbials. As such, Dixon does not remedy the above noted deficiencies of Zygmunt, Goldberg, Stark, or Oldham. Claims 32 and 58 are therefore patentable over the cited references for at least the reasons set forth above with respect to Claims 4 and 5, respectively. Claims 42, 46, 50, 54 and 56 depend from Claim 32 and Claims 43, 47, 51 and 59 depend from Claim 58. These claims are therefore also patentable over the cited references for at least the reasons set forth above with respect to Claims 32 and 58.

Claims 46, 47, 50, and 51 can be further distinguished from the cited references. In particular, these claims recite dosages of *up to 25 mg/kg/day* which dosages are substantially lower than any dosage administered to a "well" or "improved" dog in the Goldberg reference. In particular, the lowest dosage administered to a "well" or "improved" dog in Goldberg (*i.e.*, 31.6 mg/kg/day) is 26.4 percent greater than the upper limit of the dosage range recited in these claims. It is respectfully submitted that, in view of the above, the subject matter of these claims can be further distinguished from the cited references.

IX. CONCLUSION

For the foregoing reasons, the rejections of all currently pending claims should be reversed.

Respectfully submitted,

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APPENDIX - Claims on Appeal

1-3 (Canceled)

4. (Previously Presented) A method of treating an established staphylococcal infection of at least one organ or tissue selected from the group consisting of heart valve, blood, kidney, lung, bone and meninges, comprising systemically administering to a human suffering from at least one of said infections an effective amount of at least one recombinantly produced lysostaphin analogue;

wherein multiple doses of the lysostaphin analogue are administered and wherein the amount of lysostaphin analogue(s) administered from 0.5 to 30 mg/kg/day.

5. (Previously Presented) A method of treating an established infection associated with a catheter or a prosthetic device, comprising systemically administering to a human suffering from such an infection an effective amount of at least one recombinantly produced lysostaphin analogue;

wherein multiple doses of the lysostaphin analogue are administered and wherein the amount of lysostaphin analogue(s) administered is from 0.5 to 30 mg/kg/day.

6-27 (Canceled)

28. (Withdrawn) A therapeutic composition for the treatment of staphylococcal infection in humans, comprising at least one recombinantly produced lysostaphin analogue having the biological activity of proteolytic attack against glycine-containing bridges in the cell wall peptidoglycan of staphylococci and a pharmaceutically acceptable carrier, wherein the composition is suitable for systemic administration.

29-31 (Canceled)

32. (Previously Presented) The method of Claim 4, further comprising administering a second antimicrobial agent selected from the group consisting of a rifamycin, a glycopeptide and combinations thereof.

33-34 (Canceled)

35. (Withdrawn) The composition of Claim 28 further comprising at least one rifamycin or glycopeptide or combination thereof.

36-43 (Canceled)

44. (Previously Presented) The method of Claim 4, wherein the amount of lysostaphin analogue(s) administered is no more than 25 mg/kg/day.

45. (Previously Presented) The method of Claim 5, wherein the amount of lysostaphin analogue(s) administered is no more than 25 mg/kg/day.

46. (Previously Presented) The method of Claim 32, wherein the amount of lysostaphin analogue(s) administered is no more than 25 mg/kg/day.

47. (Previously Presented) The method of Claim 58, wherein the amount of lysostaphin analogue(s) administered is no more than 25 mg/kg/day.

48. (Previously Presented) The method of Claim 4, wherein the amount of lysostaphin analogue(s) administered is between 3 mg/kg/day and 25 mg/kg/day.

49. (Previously Presented) The method of Claim 5, wherein the amount of lysostaphin analogue(s) administered is between 3 mg/kg/day and 25 mg/kg/day.

50. (Previously Presented) The method of Claim 32, wherein the amount of lysostaphin analogue(s) administered is between 3 mg/kg/day and 25 mg/kg/day.

51. (Previously Presented) The method of Claim 58, wherein the amount of lysostaphin analogue(s) administered is between 3 mg/kg/day and 25 mg/kg/day.

52-55 (Canceled)

56. (Previously Presented) The method of Claim 32, wherein the at least one lysostaphin analogue is administered simultaneously with the second antimicrobial agent.

57. (Previously Presented) The method of Claim 4, wherein the at least one organ or tissue is a heart valve.

58. (Previously Presented) The method of Claim 5, further comprising administering a second antimicrobial agent selected from the group consisting of a rifamycin, a glycopeptide and combinations thereof.

59. (Previously Presented) The method of Claim 58, wherein the at least one lysostaphin analogue is administered simultaneously with the second antimicrobial agent.

60. (Canceled)

61. (Previously Presented) The method of Claim 4, wherein the infection is cleared from the at least one organ or tissue.

62. (Previously Presented) The method of Claim 4, wherein treatment results in complete sterilization of the infection.

63. (Previously Presented) The method of Claim 5, wherein the infection is cleared from the human.

64. (Previously Presented) The method of Claim 5, wherein treatment results in complete sterilization of the infection.

65. (Previously Presented) The method of Claim 4, wherein the at least one recombinantly produced lysostaphin analogue is administered to the human without a second antimicrobial agent which is not a lysostaphin analogue.

66. (Previously Presented) The method of Claim 5, wherein the at least one recombinantly produced lysostaphin analogue is administered to the human without a second antimicrobial agent which is not a lysostaphin analogue.

Docket No. 7732-022-27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: MICHAEL CLIMO, ET AL. GAU: 1633
SERIAL NO: 09/120,030 EXAMINER: BORIN, M.
FILING DATE: JULY 21. 1998
FOR: METHOD FOR THE TREATMENT OF STAPHYLOCOCCAL DISEASE

DECLARATION UNDER 37 C.F.R. § 1.132

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

I, Michael Climo, M.D., do hereby declare and state that:

1. I am one of the inventors of the subject matter claimed in the above-identified application and one of the inventors named in the above-identified application. I am a resident and citizen of the United States of America. I am not an employee of AMBI Inc., whom I understand to be the assignee of the above-referenced patent application, nor do I have any financial interest in the issuance of the above-referenced application as a patent.

2. I have reviewed the above-identified application, together with the presently pending claims. As I understand it, the subject matter claimed in the application is directed to compositions and methods for treating staphylococcal infections. The method comprises administering an effective amount of at least one recombinantly produced lysostaphin analogue. The composition comprises at least one recombinantly produced lysostaphin analogue and a pharmaceutically acceptable carrier. The recombinantly produced lysostaphin analogue has the biological activity of proteolytic attack against glycine-containing bridges in the cell wall of peptidoglycan of staphylococci.

3. I am aware of the rejection of Claims 4-5 and 28-29 under 35 U.S.C. §103(a) issued in the above-identified application in an Office Action dated June 4, 2001. In essence, the Examiner asserts that the invention claimed in these claims is obvious over Zygmunt et al., *Fortschr. Armzneimittelforsch.*, 16:309-333 or Stark et al., *N.Engl.J.Med.*, 291:239-240 or Goldberg et al., *Antimicrob. Ag. Chemother.*, 45-53 in view of Oldham et al., *J. Dairy Sci.*, 74:4175-4182.

4. I am also aware of the rejection of Claims 32 and 35 under 35 U.S.C. §103(a) issued in the above-identified application in the same Office Action where the Examiner asserts that the invention claimed in Claims 32 and 35 is unpatentable over Zygmunt et al. or Stark et al. or Goldberg et al. in view of Oldham et al. and further in view of Dixon et al., *Yale J. Biol. Med.*, 41:62-68.

5. In addition, I am aware of the rejection of Claims 33-34 and 36-55 under 35 U.S.C. §103(a) also issued in the above-identified application in the same Office Action. In essence, the Examiner asserts that the invention claimed in these claims is obvious over Zygmunt et al. and Stark et al. and Goldberg et al. and Oldham et al.

6. I have reviewed the cited reference to Zygmunt et al. Zygmunt et al. review the properties and biological activity of lysostaphin and indicate that lysostaphin is effective against staphylococcal infection in various animal models including dogs and mice.

7. I have also reviewed the cited reference to Stark et al. Stark et al. disclose treatment with a single, 500 mg dose of lysostaphin.

8. I have also reviewed the cited reference to Goldberg et al. in which Goldberg et al. discusses the treatment of experimental staphylococcal endocarditis in dogs with lysostaphin. Goldberg et al. noted that the "preliminary observations have established efficacy of lysostaphin in the early period of experimental canine endocarditis." See Goldberg et al., page 52 (emphasis

added).

9. Furthermore, Goldberg et al. teach the use of lysostaphin in the treatment of experimental canine endocarditis. This disclosure cannot be extrapolated to treatment of humans. Nor is it predictive of the efficacy of treatment in humans. This disclosure is, therefore, of limited utility in assessment of the administration of lysostaphin to humans. Unlike Applicants' present invention, therefore, Goldberg et al. fail to demonstrate eradication of a staphylococcal infection in humans. Additionally, high doses of lysostaphin were only moderately effective, as judged by the health of the dogs and by the extent of reduction in the number of bacteria in the heart valves and kidneys.

10. Both Stark et al. and Goldberg et al. are pre-1975 studies. Neither teaches or suggests that lysostaphin is effective as routine bactericide treatment in humans for systemic staphylococcal infection.

11. I have also reviewed the cited reference to Oldham et al. Oldham et al. disclose the use of recombinant lysostaphin as a "potential intramammary therapeutic" in treating bovine mastitis. See Abstract. Indeed, beginning at page 4180, Oldham et al. provide a detailed disclosure of the unusual circumstances involved in mastitis treatment, including the effect of milk on the activity of recombinant lysostaphin and the possible reasons for this effect. In the right-hand column of page 4180, the authors state that understanding the basis of reduced activity of recombinant lysostaphin in their system is essential for targeting proper therapeutic formulations. This disclosure cannot be extrapolated to treatment of humans. Unlike Applicants' present invention, therefore, Oldham et al. fail to demonstrate eradication of staphylococcal infections in humans.

12. Moreover, Oldham et al. teach only localized treatment, namely injection into the teat canal. See, e.g., Abstract. One of skill in the art would recognize that non-systemic use of recombinant lysostaphin in a non-human model is not predictive of systemic use in humans.

13. On pages 4181-4182, Oldham et al. contrast the localized treatment of bovine mastitis with previous lysostaphin studies. The authors first note that "work with nonrecombinant purified lysostaphin was reported to generate immunological problems after therapy." See Oldham, page 4181. The authors then note that while "intramammary administration to the bovine . . . [was] relatively nonimmunogenic," recombinant lysostaphin "is highly immunogenic when administered to some species parenterally in adjuvant." See Oldham, page 4182. One of ordinary skill in the art would instantly recognize, therefore, that such a highly immunogenic protein is eminently unsuitable for systemic use, which is the use ascribed to the present invention.

14. The combined teachings of the above-referenced articles would not lead one of skill in the art to produce a composition for systemically treating staphylococcal infections in humans comprising a recombinantly produced lysostaphin analogue, especially in dosage amounts less than 50 mg/kg.

15. Moreover, based on the above-referenced articles to Zygmunt et al., Stark et al., Goldberg et al., Oldham et al. and Dixon et al., one of ordinary skill in the art would not be motivated to systemically treat humans having staphylococcal infections with a recombinantly produced lysostaphin analogue.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed true. Further, I am aware that willful false statements and the like are punishable by fine or imprisonment or both, 18 U.S.C. § 1001, and that such willful false

statements may jeopardize the validity of the above-identified patent application and any patent to issue thereon.

DATE: 9/27/01

Michael Climo, M.D.